Effects of the ResQPod® on Maximum Concentration and Time to Maximum Concentration of Epinephrine in a Porcine Cardiac Arrest Model

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Abstract

Background: The ResQPod®, an impedance threshold device (ITD), was developed to augment cardiac output during cardiopulmonary resuscitation (CPR). If an ITD used with CPR does in fact increase venous return and cardiac output, then the use of such a device should increase the maximum concentration (Cmax) of epinephrine in the plasma and decrease the time to maximum concentration (Tmax). To our knowledge, no studies have investigated the pharmacokinetics of epinephrine during CPR while using the ResQPod®. The purpose of this study was to determine the effect of the ResQPod® on plasma concentrations of epinephrine in swine undergoing CPR for cardiac arrest.

Methods: This was a prospective, experimental, between-subjects design. Twelve Yorkshire-cross swine were assigned one of two groups: CPR with the ResQPod® and CPR without the use of the ResQPod®. Pigs were administered potassium chloride by intravenous (IV) route to achieve cardiac arrest. After two minutes of CPR, epinephrine was administered by IV push. Blood samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7.5 and 10 minutes after the injection of epinephrine.

Results: Results are reported in means and standard deviations respectively. Use of the ResQPod® resulted in lower Cmax than control (219.34 ± 110.59 ng/mL; 471.53 ± 349.71 ng/mL). Tmax was longer when using ResQPod® compared to the control group (4.75 ± 1.54 minutes; 3.42 ± 1.11 minutes). Although there were differences between the groups, the results were not statistically significant relative to Cmax and Tmax (p>0.276).

Conclusion: It appears the ResQPod® does not increase the delivery of epinephrine during CPR. More research is needed to evaluate the effects of the ResQPod® on epinephrine metabolite levels and on survivability. If the ResQPod® boosts the circulation of epinephrine to end organs, it is reasonable to predict that epinephrine metabolite concentrations and survivability would be higher than a control group.

Keywords

ResQPod®, ITD; Epinephrine; CPR; Swine; Concentration; Cardiac output; Cmax; Tmax

Introduction

Cardiac arrest remains one of the leading causes of mortality with more than 900 occurrences daily in the United States alone claiming an estimated 325,000 lives each year, 1,000 people a day or one person every two minutes [1]. The ResQPod®, an impedance threshold device (ITD), was developed to augment cardiac output during cardiopulmonary resuscitation (CPR). The American Heart Association (AHA) Guidelines 2005 for CPR and Emergency Cardiac Care gave the ResQPod® a Class IIa recommendation [2]. The Class IIa recommendation means the intervention has very good evidence to support its use. Conversely, the 2010 AHA Guidelines state that it was not possible to determine the relative contribution of an ITD to the improved outcome. The use of an ITD may be considered by trained personnel as a CPR adjunct in adult cardiac arrest [3].

The ResQPod® is placed between a self-inflating bag and mask or endotracheal tube during manual ventilation. The ResQPod® purportedly utilizes the interdependence of the respiratory and circulatory systems and enhances venous return and cardiac output during CPR by increasing the degree of negative intrathoracic pressure. This effect is achieved by preventing the passive inflow of air into the lungs during chest recoil between chest compressions without impeding active ventilation [4].

The use of an ITD has been shown to improve coronary perfusion pressure (CPP) anywhere from 30 to over 100% in multiple animal studies [5-11]. In addition, the ITD has improved rates of return to spontaneous circulation (ROSC) in both animal and human studies [4,9,10,12-18]. Furthermore, the use of an ITD has shown improved hospital discharge rates in multiple human studies [17,19].

The benefits of the ITD may be due to more than just its effects on CPP. It is possible that the improved ROSC and hospital discharge rates are also due to improved circulation of emergency medications delivered during cardiac arrest. The 2010 AHA guidelines state that 1 mg of epinephrine should be given after two minutes of CPR and every 3-5 minutes thereafter. If the use of an ITD during CPR does in fact increase venous return and cardiac output, it stands to reason that the use of such a device would improve the circulation of epinephrine in a cardiac arrest model. To our knowledge, there are no studies that have examined the pharmacokinetics of epinephrine given during CPR with an ITD. The purpose of this study was to determine the effect of the ResQPod® on plasma levels of epinephrine in swine undergoing CPR for cardiac arrest.

Methods

This study was a prospective, experimental between-subjects design. The protocol was approved by the Institutional Animal Care and Use Committee (IACUC), and the animals received care in compliance with the Animal Welfare Act, the Guide for the Use of Laboratory Animals. Twelve Yorkshire-cross swine weighing between 70-80 kg were equally assigned by the use of computer generated numbers (n=6 per group) to one of two groups: CPR with the ResQPod® and CPR without the use of the ResQPod®. To avoid any variability in subjects, the investigators purchased the pigs from...
the same vendor, used pigs approximately the same size, and used only male pigs. The rationale for using male pigs was to avoid any potential hormonal effects. The swine were fed a standard diet and observed for three days to ensure a good state of health; the subjects where NPO after midnight the day before the experiment.

Anesthesia was induced with an intramuscular injection of Telazol (4-8 mg/kg) and inhaled isoflurane 4%-5%. After placement of an endotracheal tube, the investigators reduced the isoflurane concentration to a maintenance dose (0.5-2%) for the remainder of the experiment. A peripheral IV was started on all subjects. Normal saline (NS) was administered at keep vein open (KVO) rate to maintain patency. The animals were ventilated at 8-10 ml/kg tidal volume with a standard Narkomed anesthesia machine (Drager, Telford, Penn.) with an initial respiratory rate of 10-14 breaths per minute. The swine were continuously monitored with the following standard monitors: HR, BP, ECG, SpO2, ETCO2, and temperature. A catheter for collection of blood specimens was inserted into the left carotid artery using a cut-down technique. Potassium chloride 20 mg/kg was then administered via the IV and flushed with 10 ml of normal saline. The electrocardiogram (EKG) tracing was observed for any non-perfusing rhythm (ventricular fibrillation, pulseless ventricular tachycardia, or asystole) indicating that the pig was in cardiac arrest. Upon recognition of a non-perfusing rhythm, the investigators discontinued anesthesia. The pig was allowed to stay in arrest for two minutes.

After the two-minute period, CPR was initiated with a mechanical CPR device, the “Thumper” (Michigan Instruments, Inc.). The “Thumper” was used to automatically compress the sternum at a predetermined depth of 1-1/2 inches at a rate of 100 beats per minute according to the guidelines of the AHA. The Thumper was used to ensure that the rate and depth of compression where consistent over time and reproducible from animal to animal. The ResQPod® group had the device placed on the endotracheal tube in accordance with the manufacturer’s instructions.

Compressions with ventilations with 100% oxygen were continued at a ratio of 30:2. After one minute of CPR, an initial baseline blood specimen was collected from the arterial line followed by a 10 mL normal saline flush for all groups. One mg of epinephrine diluted in 10 mL of normal saline was administered by IV push in one second or less and followed by a 10 mL normal saline flush. In addition to the baseline sample, blood samples (10 mL) were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7.5 and 10 minutes after the epinephrine injection. Before each sample was collected, 5 ml of blood was discarded.

All plasma samples were sent to the University of Washington Pharmacokinetics Laboratory, Seattle, Washington, for analysis. The analysis of epinephrine in the plasma was performed by the high performance liquid chromatography with mass spectrometry-mass spectrometry (HPLC-MS/MS) as described by Zhang et al. [20]. Maximum plasma concentration (Cmax) and time to maximal concentration (Tmax) were determined directly from the plasma concentration-time data.

Statistical Analyses

A Multivariate Analyses of Variance (MANOVA) was conducted on pre-intervention data that included weight and vital signs. In addition, a MANOVA was used to test for significance the difference between the two groups (CPR with and without the ResQPod®) on two response variables: Cmax and Tmax.

Results

The MANOVA indicated that there were no significant differences in the pre-intervention data (p > 0.05) indicating the groups were equivalent on those parameters. The Cmax with the ResQPod® group was less compared to the group without the ResQPod®. However, the Wilks Lambda, the test statistic for the MANOVA, indicated there were no statistically significant differences between the groups relative to either Cmax and or Tmax (p=0.276). The results are summarized in Table 1.

Discussion

We expected that the ResQPod® would enhance delivery of epinephrine to the central circulatory system during CPR. Therefore, the ResQPod® would increase venous return and cardiac output, which would decrease the time to maximum plasma concentration of the circulating epinephrine. The effect of using an ITD during CPR on Cmax is less predictable. On one hand, it should enhance delivery of drug from the periphery more effectively and increase plasma concentrations. However, enhanced cardiac output would also increase distribution resulting in lower plasma concentrations. In addition, it would increase liver blood flow, thereby increasing metabolism resulting in lower plasma levels of the parent drug. In future studies the impact of metabolism could be determined by measuring plasma metabolite levels. However, in the timeframe of this experiment (10 minutes), distribution would be expected to have greater impact on plasma concentration than metabolism.

The results of our study suggest that the use of the ResQPod® during CPR does not enhance drug circulation and does not appear to increase cardiac output. Although, numerous studies support improved CPP and improved ROSC rates, there are studies that found no improvement of CPP and have demonstrated a statistically significant reduction in ROSC rates when using an ITD. Menegazzi et al. offer a number of interesting explanations for their observation that ROSC rates decreased when using the ITD to include a theory that passive ventilation that normally occurs with chest compression/relaxation is eliminated resulting in hypoventilation [21]. When discussing the limitations of their study, they stated that it was possible that the use of the “Thumper” did not allow for complete chest recoil. Hence, this may have adversely affected the functionality of the ITD. The present investigation also used a “Thumper” and if this is true, it may have also adversely affected the function of the ITD in our study. Nevertheless, the manufacturers of both the Thumper and the ResQPod® do not specify that these should not be used in combination.

In conclusion, this study compared the Cmax and Tmax of Epinephrine.

### Table 1: Result of Cmax and Tmax of Epinephrine.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± Standard Deviation</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax with ResQPod®</td>
<td>219.34 ± 110.59 ng/mL</td>
<td>6</td>
</tr>
<tr>
<td>Cmax without ResQPod®</td>
<td>471.53 ± 349.71 ng/mL</td>
<td>6</td>
</tr>
<tr>
<td>Tmax in minutes with ResQPod®</td>
<td>4.75 ± 1.54</td>
<td>6</td>
</tr>
<tr>
<td>Tmax in minutes without ResQPod®</td>
<td>3.42 ± 1.11</td>
<td>6</td>
</tr>
</tbody>
</table>

Cmax refers to the maximum concentration of the plasma epinephrine; Tmax refers to the time to maximum concentration of plasma epinephrine in minutes; Ng refers to nanograms and mL refers to milliliters.
epinephrine in a cardiac arrest swine model using the ResQPod® with CPR compared to CPR without the ResQPod®. A major limitation of this study was that cardiac output was not measured. Future research needs to be implemented investigating $C_{\text{max}}$ and $T_{\text{max}}$ in a cardiac arrest model with the addition of monitoring cardiac output. In addition, more research is needed to evaluate the effects of the ResQPod® on survivability and serum epinephrine metabolite levels. If the ResQPod® boosts the circulation of epinephrine to end organs, it is reasonable to predict that epinephrine metabolite concentrations and survivability will both increase.

References


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